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Health economics of blood transfusion safety – focus on sub-Saharan Africa

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ABSTRACT

Background and objectives: Health economics provides a standardised methodology for valid comparisons of interventions in different fields of health care. This review discusses the health economic evaluations of strategies to enhance blood product safety in sub-Saharan Africa.
Methods: We reviewed health economic methodology with special reference to cost-effectiveness analysis. We searched the literature for cost-effectiveness in blood product safety in sub-Saharan Africa.
Result: HIV-antibody screening in different settings in sub-Saharan Africa showed health gains and saved costs. Except for adding HIV-p24 screening, adding other tests such as nucleic acid amplification testing (NAT) to HIV-antibody screening displayed incremental cost-effectiveness ratios greater than the WHO/World Bank specified threshold for cost-effectiveness. The addition of HIV-p24 in combination with HCV antibody/antigen screening and multiplex (HBV, HCV and HIV) NAT in pools of 24 may also be cost-effective options for Ghana.
Conclusions: From a health economic viewpoint, HIV-antibody screening should always be implemented in sub-Saharan Africa. The addition of HIV-p24 antigen screening, in combination with HCV antibody/antigen screening and multiplex (HBV, HCV and HIV) NAT in pools of 24 may be feasible options for Ghana. Suggestions for future health economic evaluations of blood transfusion safety interventions in sub-Saharan Africa are: mis-transfusion, laboratory quality and donor management.

1. Introduction

Blood transfusion can be a life saving medical intervention [1]. This is certainly the case in developing countries where conditions requiring transfusion are often associated with high mortality and morbidity when transfusion is not available [2]. As with all medical interventions, blood transfusion not only brings benefits to patients, but may come at the expense of side-effects ranging from mild fever to death caused by acute haemolytic reactions [3–5]. The side-effect that is most often documented in relation to blood transfusion is the transmission of blood borne infections. Very important in this respect is the spread of HIV in populations since the early 1980s. Although the disastrous transmission of HIV in the era before donor deferral and screening springs to mind, the disease burden inflicted world wide by transfusion-related hepatitis may surpass that of HIV [6,7]. In the developed world, the risk of transmission of HIV, hepatitis B virus (HBV) or hepatitis C virus was greatly reduced over the last decades by donor deferral, the use of more sensitive screening methods and pathogen inactivation of plasma derived medicinal products [3,8–12]. The perception of the risk of blood borne infections and potential judicial consequences has prompted decision makers to further maximise transfusion safety with regard to the transmission of pathogens [13–15]. Currently, bacterial contamination of platelets, immune system-related side-effects, fluid overload and, last but not least, transfusion medicine errors pose a greater risk to the health of patients receiving a blood transfusion in the developed world than do HBV, HCV or HIV [3,16–18].

Developing countries are faced with specific problems which endanger the provision of sufficient safe blood to patients requiring transfusion [19]. Less than 40% of the donations world wide are donated in developing countries (low and medium human development index; HDI) where more than 80% of the world population lives. To support the unstable balance between supply and demand in the blood banks of the developing world, less than 25% of the donations are from voluntary unpaid regular donors [20]. Mostly,

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the transfused blood is replaced by donations taken from family members, friends or others, with or without payment [21]. Such replacement donations have a higher risk of, for example, HIV infection than the WHO-recommended, unpaid voluntary regular donors [22]. The main reason that the replacement system has continued over the last 20 years is that the direct costs are 3–5 times lower compared with the unpaid voluntary regular donor system [21]. Further increasing the risks, routine screening of donations for HIV, HBV, HCV and syphilis is not yet fully implemented in all developing countries [20].

2. Principles of cost-effectiveness analysis and health economics

The methodology of cost-effectiveness analysis and health economics has been discussed in detail in recent review papers [23–26]. The main study types used in economic evaluation are cost-effectiveness (CEA) and cost–utility analysis (CUA) in which the incremental net costs of a programme are related to the incremental health benefits.

CEAs measure health effects in physical units such as increments in life-years gained, infections averted, cases found, cases cured, etc. Cost-minimisation analysis (CMA) is a specific form of cost-effectiveness analysis whereby the health effects of the intervention and the current practice are equivalent (or are expected to be equivalent). In CUA, the incremental life-years gained are adjusted for quality of life, to arrive at a common measure known as quality adjusted life-year (QALY). For developing countries, disability adjusted life-years (DALY) averted are often used as burden of disease measure. DALYs are estimated by adding the years of life lost due to the disease and the adjusted years lived with disease. Costs are measured in monetary units. Cost-effectiveness or cost–utility ratios are expressed as net costs per unit of effect by comparing the new intervention with current practice (incremental analysis).

Depending on the perspective of a health economic evaluation, different types of costs are considered. Generally, all health economic analyses include direct costs for medical care borne by the health system, community and families of patients. Direct costs can either be program-related, such as tests in a screening programme or can be patient-related, such as hospital, outpatient and community care. Health economic analyses performed from the health-care providers' perspective tend to focus on direct costs only. The current consensus in health economics is that a more complete model is achieved with the use of a societal perspective and therefore that all relevant costs and consequences for society should be considered, including productivity and leisure losses [27]. However, discussion remains whether loss of productivity caused by morbidity and mortality should be incorporated as indirect costs or as quality adjustments in cost–utility analysis [28–33], and how to exactly measure indirect costs using human capital or friction costing approaches. Patient-related costs– direct as well as indirect– may transfer to benefits if illnesses and related costs are averted, for example through screening or inactivation procedures of blood products. The basic concept in health economic analyses is to evaluate the net costs, i.e. programme costs minus patient-related benefits. From a health economic viewpoint any new programme with negative net cost (offering overall cost saving programs)– and non-negative health gains– should be implemented since it is a dominant strategy. Positive net cost should be related to health gains such as life-years gained. To determine whether implementation is justified, the cost-to-health-gains (cost-effectiveness) ratio should be carefully considered and compared to acceptability thresholds, if available. The threshold for health economic acceptability has been published at US$50,000 per QALY gained in the USA [34]. According to WHO and World Bank guidelines, strategies that show a cost-effectiveness ratio below the per capita gross national income (GNI) are regarded as cost-effective, whereas strategies with cost-effectiveness ratio above three times the per capita GNI are regarded as not cost-effective [35,36]. As viral infections often involve serious complications requiring complex health-care interventions occurring several years after infection, the concept of discounting future costs is relevant. Examples of long-term complications are cirrhosis after years of chronic hepatitis or development of AIDS in the late stage of HIV infection. Discounting is a method to adjust future costs and benefits to their present value (cost and benefits are less weighted the further in the future they accrue). The discounting procedure applies two major principles. Firstly, capital invested in a new technology could have been invested otherwise and may have gained interest. Secondly, there is a pure time preference with short-term benefits being preferred to future benefits with respect to uncertainty as to whether one will be able to benefit from the monetary amount next year as one is now. The value of the discount rate should be chosen in accordance with marginal rates on investment and market interest rates. Many countries use average interest rates of long-term government bonds [37]. Often, discount rates are specified in the national guidelines for health economic research and vary between, for example, 1.5% for the Netherlands, 3% in the USA, and 6% as previously used in the United Kingdom [27].

Sensitivity analysis is an important tool to investigate the outcomes obtained from health economic models. Whereas most parameters used in the models are derived from clinical trials or from retrospective data sources, others may be based on individual expert opinions. Often, few parameters are known with a high degree of undisputed accuracy. To estimate the effect of uncertain variables on the robustness of the model results, sensitivity analysis is performed.

3. Study characteristics and health economic aspects

We searched MEDLINE for combinations of MESH(sub)-heading "blood transfusion", "cost(-)effectiveness" or "cost(-)utility", "developing", "Africa", "low-HDI". We included health economic evaluations on blood transfusion safety strategies using outcome measures expressed in net cost per life-year or per QALY gained, DALY averted or infections prevented. Additionally, cost(-minimisation) analyses that indicate net cost savings were also selected. Net cost savings do not necessarily require a full health economic analysis in the absence of negative health gains. Only studies from sub-Saharan Africa were selected.

The MEDLINE search yielded nine studies that matched our selection criteria. Unfortunately, two potentially interesting papers; one on malaria screening [45] and one on HIV screening and deferral [46], could not be retrieved for full review. In total seven papers were reviewed (Table 1). HIV screening, only or in combination with other safety strategies, was the most encountered subject for health economic evaluation. HIV screening strategies were evaluated in six out of seven selected papers. Strategies reducing the risk of HBV or HCV transmission were evaluated in two studies.

In the early papers, before 2000, the study type was stated as cost–benefit analysis. Formally, in cost–benefit analysis health effects are transformed to monetary units. None of the included studies transformed health gains to monetary units. Also, none of the selected studies before 2000 used the net costs framework. For instance, Foster and Buvé [38] separated the costs of screening for HIV and the financial benefits of preventing HIV infection. The resulting cost savings of HIV screening were expressed as a benefit

Table 1
Study characteristics and health economic aspects of the selected studies.

Safety strategy	Country	Year	Type	Measure	Perspective	Discounting	
						M (%)	H (%)
HIV screening [38]	Zambia	1991	CEA	US$/LYG	Health care	3	0
HIV screening [39]	Zaire	1992	CEA	US$/IP	Health care	n.i.	n.i.
HIV screening, more voluntary donations, reducing transfusions, autologous transfusions, laboratory quality [40]	Tanzania	1992	CA	US$	Health care	5	5
HCV screening [41]	Uganda	1999/2000	CEA	US$/IP	n.i.	n.r.	n.r.
HIV screening [42]	Chad	1999	CEA	US$/IP	n.i.	n.i.	n.i.
HIV screening [43]	Ghana	2004	CUA	US$/DALY	Societal	3	3
HBV, HCV and HIV screening [44]	Ghana	2007	CUA	US$/DALY	Health care	3	3

Abbreviations: CA, cost analysis; CEA, cost-effectiveness analysis; CUA, cost–utility analysis; HCV, hepatitis C virus; H, health; HIV, human immunodeficiency virus; IP, infection prevented; LYG, life-year gained; M, monetary; n.i., not included; n.r., not required because of short-term time frame.

to cost ratio. One of the selected papers applied the preferred societal perspective in the analysis. The perspective of the health-care provider was the most utilised viewpoint (four out of seven). In two papers the perspective was not specified or could not be determined from the paper.

Univariate and/or multivariate sensitivity analysis was carried out in six out of seven studies. Discounting of costs was performed in four of seven health economic evaluations. In three out of the seven analyses, health benefits were discounted.

4. Results

All papers reporting on the cost-effectiveness of post-donation HIV-antibody screening in sub-Saharan Africa show that HIV screening gives health gains and saves costs (Table 2). New HIV infections prevented by HIV-antibody screening ranged from 150 to 1400 per 10,000 donations. Obviously, the number of new HIV infections prevented depended strongly on the HIV prevalence in blood donors and the prevalence of HIV infection in transfusion recipients. The incremental cost of HIV-antibody screening seems to have decreased over the last decade, improving the health economic profile of HIV-antibody screening even further.

Only two health economic evaluations were found which evaluated the use of more sensitive HIV antigen tests, such as p24 or NAT, in addition to HIV-antibody screening in sub-Saharan Africa. Both evaluations were carried out in Ghana and conducted by the authors of this review. One evaluating multiplex screening for HBV, HCV and HIV will be discussed later. The number of new HIV infections prevented by p24, NAT in minipools of 24 samples (MP24-NAT) and individual donation NAT (ID-NAT) in addition to HIV-antibody screening were 0.7, 1.5 and 1.95 per 10,000 donations, respectively [43]. The number of new infections prevented by

Table 2
Risk reduction and health economic implications of improving blood transfusion safety.

Safety strategy	Country	Year	Risk intervention[a]	Risk comparator[a]	Infections prevented[a]	Incremental cost/donation (US$)	Outcome
HIV screening [38]	Zambia	1991	106	1892	1398	4.42	Cost saving, BCR 2.7/1
HIV screening [39]	Zaire	1992	n.s.	265–529	n.s.	9.12–18.56	171–349 US$ test costs/ prevented HIV + donation
HIV more voluntary donations, reducing transfusions, autologous transfusions, laboratory quality [40]	Tanzania	1992	64	98	155[b]	12.41[d]	Cost saving, BCR ranging from 3.1/1 to 6.6/1
HIV screening + more voluntary donations, reducing transfusions, autologous transfusions, laboratory quality [40]	Tanzania	1992	64	801[c]	864[b]	12.41[d]	Cost saving, BCR ranging from 16/1 to 37/1
HCV screening [41]	Uganda	1999/2000	n.s.	58	62–77	5.95	782–938 US$ per HCV infection prevented
HIV screening [42]	Chad	1999	78	778	1400	12.23	87 US$ per HIV infection prevented
HIV-Ab vs no screening [43]	Ghana	2004	2.76	151	241	5	Cost saving, BCR 10/1
HIV-p24 vs Ab [43]	Ghana	2004	2.04	2.76	0.7	2	1237 US$/DALY averted
HIV MP24-NAT vs p24 [43]	Ghana	2004	1.22	2.04	1.5	5.5	2248 US$/DALY averted
HIV ID-NAT vs MP24-NAT [43]	Ghana	2004	0.76	1.22	1.95	7.5	3508 US$/DALY averted
HIV-p24, + HCVAgAb + HBsAg vs HIV-Ab + HCV-Ab HBsAg [44]	Ghana	2007	n.s.[e]	n.s.[e]	1.41 (HIV) 2.18 (HCV)	1.60	608 US$/DALY averted
MP24 multiplex NAT vs HIV-p24, + HCVAgAb + HBsAg [44]	Ghana	2007	n.s.[e]	n.s.[e]	1.59 (HIV) 0.24 (HCV) 0.00 (HBV)	16.40	1154 US$/DALY averted
MP6 multiplex NAT vs MP24 multiplex NAT [44]	Ghana	2007	n.s.[e]	n.s.[e]	0.42 (HIV) 0.06 (HCV) 0.95 (HBV)	13.00	2468 US$/DALY averted
ID multiplex NAT vs MP6 multiplex NAT [44]	Ghana	2007	n.s.[d]	n.s.[d]	0.48 (HIV) 0.06 (HCV) 0.12 (HBV)	24.60	8306 US$/DALY averted

Abbreviations: Ab, antibody; BCR, benefit to cost ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ID, individual donation; MP, minipool of 6 or 24 donations; n.i., not included; n.s., not specified.

[a] Per 10,000 donations.

[b] Reduction of transfused patients (from 3000 to 1200) gave extra reduction of HIV transmission.

[c] Similar costs were assigned by the authors.

[d] Crude HIV transmission risk was 1200 per 10,000 donations before introduction of HIV screening and more voluntary donations, reducing transfusions, autologous transfusions, laboratory quality.

[e] Parameters can be found at http://www.bloodsafety.info.

HIV-antibody screening in this setting was expected to be 241 per 10,000 donations. In combination with the high additional cost of the more sensitive tests and the low yield of prevented HIV transmissions, the resulting incremental cost-effectiveness ratios (ICERs) are relatively high compared to HIV-antibody screening. In 2008 the GNI per capita of Ghana was US$670 (US$480 in 2004) [47,48]. Therefore, the World Bank/WHO threshold for cost-effectiveness (three times the GNI per capita) was US$2010 in 2008 (US$1440 in 2004). Only HIV-p24 antigen screening was below the specified threshold for cost-effectiveness for Ghana in 2004.

Very few data are available on the cost-effectiveness of screening blood donations for viruses other than HIV in sub-Saharan Africa. For Uganda it was estimated that HCV screening of blood donation would cost US$782–938 per new HCV infection prevented. However, saved health-care costs by preventing HCV infection were not included in this study.

Using a health economic model which is accessible by a Web interface (http://www.bloodsafety.info), the residual risk of transmission and the cost of screening were estimated for five post-donation screening strategies for Ghana [44]:

(1) HBsAg, HCV-Ab, and HIV-Ab;
(2) HBsAg, HCV-Ab + Ag (HCV combo), and HIV-Ab + p24 (HIV combo);
(3) MP24-NAT (pool of 24 donations on HBV, HCV, and HIV) + HIV-Ab, HCV-Ab, and HBsAg;
(4) MP6-NAT (pool of six donations on HBV, HCV, and HIV) + HIV-Ab, HCV-Ab, and HBsAg; and
(5) ID-NAT (on HBV, HCV, and HIV) + HIV-Ab, HCV-Ab, and HBsAg.

Strategies were compared to the next least expensive strategy, for instance (2) versus (1), (3) versus (2), (4) versus (3), etc. Compared to HIV-p24 screening alone, the combination of this test with HCV combo seems to be a more cost-effective strategy. Also, multiplex (HBV, HCV and HIV) minipool NAT screening in pools of 24 seems to be more cost-effective than HIV MP24-NAT alone. Both strategies (2 and 3) were also below the World Bank/WHO three times the GNI per capita threshold for cost-effectiveness of US$2010 in 2008.

5. Discussion

Blood donation screening for HIV-antibody to prevent HIV infection in sub-Saharan Africa is a strategy which saves costs and provides health gains [38]. Therefore, from a health economic viewpoint, HIV-antibody screening should always be implemented. Similar to high-HDI countries, more sensitive tests added to HIV-antibody, HCV antibody and HBsAg screening are generally associated with higher ICERs. More than three times the GNI or GDP per capita is needed to save one DALY for MP6 and ID-NAT. However, compared to high-HDI countries, the ratio of GNI or GDP to the cost-effectiveness ratio is considerably lower. The ratio of the ICER to the GNI of ID multiplex NAT compared to MP6 multiplex NAT was 18.5 versus over 1600 for Ghana and the Netherlands, respectively [44]. This difference is explained by the young average age of the transfusion recipient and, obviously, the higher risk of viral transmission. Using NAT in addition to serological screening for HBV, HCV HIV is probably not cost-effective for Ghana, although multiplex MP24-NAT may be an exception. Moreover, using NAT in blood bank screening was also not shown to be cost-effective to enhance HIV screening in a cross-section of African countries [49]. Antigen screening used in combination with antibody screening for HIV and HCV may be a cost-effective option for some countries.

Blood supply systems in high-HDI countries provide a very high level of product safety with regard to transfusion transmitted infection. Implementing these systems in developing countries appears to be an attractive solution to improve blood transfusion [50]. However, we must remember that the costs of achieving such systems and maintaining these levels of safety in developed countries are very high. The societal cost of transfusing two units of RBC in The Netherlands (US$400–500) exceeds the GNI per capita in the majority of the low-HDI countries. Blood supply systems in developing countries are gradually moving from hospital-based blood banks, heavily dependent on replacement donors, to more consolidated and nationally supported systems relying on voluntary donors. In general, the unit costs of blood products from consolidated blood supply systems are higher than those from hospital-based blood banks [51]. Most consolidated blood supply systems in African countries receive external funding [51]. The dependence on external funding hampers the sustainability of these consolidated blood supply systems. Preliminary data showed that an alternative hospital-based screening strategy using pre-donation rapid test screening in combination with minipool NAT on HBV, HCV and HIV may be cost-effective [52]. Pre-donation rapid tests for HBV, HCV and HIV in combination with post-donation NAT cost less and prevent more loss of health than post-donation serological screening.

The contribution of human error to the risk of pathogen transmission is reported to be very low in high-HDI countries [53]. In low-HDI countries, however, what little data there are, indicate that human error can contribute up to 20% of the HIV transmission risk [54,55]. An overview of interventions improving transfusion safety in a selection of African countries revealed that interventions reducing human error in screening and processing of blood donations were cost-effective [49]. Because of the lack of data on human error, we designed a prospective study to investigate the contribution of human error to pathogen transmission in low-HDI countries [56]. The study yielded useful and interesting observations, although the original goals of the research plan were not reached. We found that infectious disease marker screening was not performed within the required time after blood donation. Furthermore, collection and storage conditions of samples were not according to specifications. Also, volume variations, poor labelling and haemolysis of the blood samples were noted. Nevertheless, the problems encountered do also indicate that human error augmented by absence of a working quality system will contribute to pathogen transmission in low-HDI countries.

Enhancing blood transfusion safety in low-HDI countries by introducing more sensitive high-tech tests is maybe not cost-effective. Nevertheless, transfusion recipients in low-HDI countries, who are mainly children and young women, face a substantially higher probability of HBV, HCV and HIV infection compared to transfusion recipients in high-HDI countries. From the papers included in this review, directions for cost-effective improvements in transfusion safety in low-HDI countries can be discerned. For some regions it may be worthwhile to investigate whether pre-donation screening in combination with in-house NAT is cost-effective. Preliminary data indicate that investments in donor management to motivate low-risk voluntary non-remunerated donors to donate blood are cost-effective. Also, investments in laboratory performance and quality systems to achieve a reduction of human error may prevent considerable disease burden in transfusion recipients [57]. Overall, however, the inadequate supply of safe blood is regarded as the greatest threat to blood transfusion safety in low-HDI countries [20].

6. Future perspectives

The cost-effectiveness of preventing transfusion transmitted HBV, HCV and HIV infection with screening is well studied in

high-HDI countries. However, health economic evaluation is still needed to provide decision makers with insights into the costs and consequences of adopting new screening strategies for emerging pathogens [58–60]. Health economics of donor-related interventions, such as temporary exclusion or motivating specific low-risk donor groups to donate, are scarce and more research is warranted in this important area of blood transfusion safety [61,62]. Health economic evaluations can also be used when new technology to inactivate pathogens in red blood cell concentrates or whole blood becomes available [63]. Currently, transfusing the wrong unit to the wrong patient causes the greatest disease burden in The Netherlands and other developed countries [64–66]. Also for developing countries mis-transfusion may contribute to a high disease burden. Health economic evaluations of available measures to prevent these mis-transfusions in developing countries, such as wristband patient identification, could motivate decision makers to develop legislation and make funds available to introduce these safety barriers in clinical practice [67,68]. For low- to medium-HDI countries, further research in the health economics of improving blood transfusion safety by screening strategies for HBV, HCV and HIV is needed to inform decision makers. Special attention should be given in these evaluations to the sustainability and technical feasibility of the proposed screening strategies. Sustainability and affordability should also be considered from the perspective of the payer, which is often the family of the patient in low-HDI countries. Health economics of donor-related interventions, such as using donor management to motivate regular voluntary non-remunerated donors, is of particular importance in low-HDI countries. Preliminary data showed that room for improvement exists in laboratory standards [57]. The quality of blood grouping performed in the blood bank laboratory is as essential for the safety of the blood transfusion as screening donations for pathogens. The costs and consequences of replacing error prone manual blood grouping by more sophisticated techniques in low-HDI countries may be worthy of exploration.

As science progresses and new evidence comes available, economic models require updating. The time to publication of the results of a health economic evaluation is considerable. Often, estimates used in the health economic evaluation quickly become outdated, thus invalidating the results of the health economic evaluation. Sometimes, updates of health economic evaluations appear as brief reports which lack sufficient detail for proper interpretation. These problems can be overcome by disseminating health economic evaluations on the internet as well as in peer-review journals. In fact, all peer-reviewed journals should stimulate authors to publish their models with associated technical appendices online, in order to promote the transparency of health economic models. Often, health economic models are regarded as a 'black box'. Online publication of health economic models enhances transparency since the quality of the models can be scrutinised by peers.

Conflict of interest statement

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